## Pharmacogenomics and clinical applications

**Summary:** This program seeks to anticipate ethical issues with new types of tests (pharmacogenomics) and tests used in new contexts (primary care risk assessment), related to developing thresholds for public availability and to evaluating communication about the benefits and risks of genetic tests.


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**Background:** The integration of genetic tests into clinical practice is occurring rapidly. The forces driving this trend include professional opinion, legal concerns, consumer interests and the market. State health departments have been increasing the number of diseases assessed in newborn screening. The American College of Obstetricians and Gynecologists (ACOG) has recommended that pregnant women be offered cystic fibrosis carrier testing. The first large scale direct-to-consumer marketing of a genetic test, BRCA testing, began in September 2002 in Denver and Atlanta. Pharmacogenomic testing to predict safety and efficacy of pharmaceuticals can be expected to increase.

However, primary care providers are far from fully integrating genetic tests into their repertoire of risk assessment and risk reducing interventions for a variety of reasons. Many physicians have limited training and experience interpreting genetic tests. In the primary care setting, there is limited time to engage patients in complex education about genetics. In fact, recent studies have demonstrated that primary care physicians sometimes are inappropriately ordering tests, and not providing adequate interpretations However, it is in the

primary care setting that genetic tests have the potential to have the greatest impact on health outcomes.

Because of the current climate of clinical genetic testing, it is important to critically examine questions about which new tests should be introduced and what criteria should be used to make these decisions. The Secretary's Advisory Committee on Genetic Testing (SACGT) endorsed an approach to this question based on empirical evidence about analytic validity, clinical validity, and clinical utility. Our prior work in this area has been to articulate an "evidentiary" model that argues that evidence is necessary but not sufficient, to emphasize explicitly acknowledging and discussing normative issues in these deliberations. More recently, we have been applying this approach to specific case studies including cystic fibrosis carrier testing, cystic fibrosis newborn screening, and pharmacogenomics testing.

Clinical utility (the likelihood that genetic tests will improve clinical outcomes) can offer a very compelling justification for the introduction of new tests. However, there are limited data to support the clinical utility of many genetic tests. Before primary care clinicians routinely adopt new genetics tests, it will be necessary to understand their impact on health. Previously, a high risk of serious harm that could be avoided by an effective intervention, as exemplified by PKU screening, has been the paradigm for the impact of genetics on health. In contrast, much of primary care practice is premised on improving public health by identifying people who have a relatively increased risk (even if absolute risk is low) and offering interventions to reduce relative risk (but not eliminate it). Cholesterol screening for cardiovascular disease exemplifies this paradigm.

How will genetics fit into the primary care risk reduction paradigm? To address this question, we are conducting a pilot study of a genetic and environmental risk assessment (GERA) on risk reduction behavior. This pilot study will assess the impact of testing for MTHFR (Methylenetetrahydrofolate reductase) alleles and folate levels on colon cancer screening behavior in a primary care population of >50 year old adults. Colon cancer screening behavior was chosen because of the consensus about its clinical value in this population. While there are no data about the impact of MTHFR testing in this context, such testing is already available commercially over the Internet.

Traditionally, when new genetic tests were offered, (i.e. CF carrier testing, Huntington Disease) extensive informed consent process has been developed to accompany the tests. However, it will not be feasible to use this robust model for all new tests. Thus, it is important to conceptually articulate which characteristics of tests should influence the informed consent process and in what way. Understanding the relationship between tests characteristics and informed consent will be increasingly important as more unrelated tests are added to "multiplex" panels. The project on informed consent for clinical genetic testing is based on involvement with the Informed Consent Working Group of the

Secretary's Advisory Committee on Genetic Testing (SACGT). The GERA pilot study examines the effectiveness of one approach to informed consent.

Much of communication about genetic disease, however, occurs outside of the informed consent context. In the clinical context, if often occurs in the context of treatment decisions. These decisions can be influenced by clinicians' and patients understanding of specific disease. To understand this issue, we have explored the variability of descriptions of cystic fibrosis in carrier testing leaflets. This study illustrated the normative dimension of disease descriptions. It is important to be explicit about these normative aspects in order to reflect on which normative messages are desired.

Communication also occurs outside the clinical context; in journalism, fiction, and advertising. While each of these may be important in shaping the public's collective and individual understanding of genetics, communication designed to market genetic tests is more likely to have direct influence on clinical interactions.

**Objectives:**

1) To identify the ethical issues that should influence when new tests are introduced into clinical practice

2) To evaluate the impact of a modestly predictive genetic test to influence patient behavior in a primary care setting

3) To develop a framework to tailor the informed consent process to genetic testing characteristics

4) To consider the ethical implications of the impact of language to influence understanding about genetics

**Methodology**

**Objective 1:** The articulation of the normative issues in health policy decisions for the introduction of new genetic tests has been a conceptual project. Cystic fibrosis carrier testing and newborn screening have been interesting case studies because of the variety of policy approaches taken. In some geopolitical regions, both carrier testing and newborn screening are offered. Others only offer one or the other is offered, and in some places neither is offered. This diversity has allowed us to ask the question about whether these different policy responses are based on different normative considerations. However, rarely are such normative considerations explicitly expressed.

For example, the 1997 NIH Consensus Development Conference recommended that CF carrier testing be routinely offered, but did not articulate a normative justification. CF newborn screening is currently offered in six states. However the specific strategies suggest that there has been little attention to the

complexity of normative issues to be addressed (i.e. balance of benefits and risks to false positive families).

Consideration of pharmacogenomics testing has allowed us to ask questions about what features of a testing scenario raise ethical concerns, by focusing on how pharmacogenomics testing is similar or different to other genetic testing situations.

**Objective 2:**The Genetic and Environmental Risk Assessment (GERA) pilot study will begin this fall and will involve 60 adults who will be offered GERA testing in a primary care setting. They will receive a two-page pamphlet on GERA and meet with a nurse for about 10 minutes. The nurse will offer "decision-counseling" with the aid of a PDA (personal digital assistant) to help people identify their value preferences. This provides an opportunity for patients to consider whether their decision about testing is consistent with their expressed preferences. We will survey attitudes about colon cancer, screening, and genetic testing before and after the GERA offer. The main objective is to measure the effect size of the uptake of GERA, and its impact on potential screening behavior to assist in designing a study powered to assess if GERA decision counseling and/or GERA testing has an impact on screening behavior.

**Objective 3**: The objective of the SACGT Working Group had been 1) identify the characteristics of genetic tests that are relevant to informed consent, 2) to describe how to tailor informed consent based on these characteristics, and 3) to articulate mechanisms for oversight to insure that an appropriate informed consent process is followed. Our project focuses on the first two objectives and has been influenced by our participation in The SACGT process. However, we have diverged from the Working Group in our answers to these questions.

**Objective 4:** Language to describe genetic diseases and associated moral deliberations can have an impact on clinical interactions. We have conducted two conceptual explorations of this issue. First, we have looked at the moral implications of teaching about ethical dilemmas on reproductive decision-making using hypothetical situations. Specifically, we have considered the impact of describing a case of a couple with achondroplasia that wishes to use prenatal diagnosis to have a child who also has achondroplasia. Second, we have examined the use of the term, "lethality", which is used as a clinical description, and articulate its normative dimensions.

The language used in advertisements raises concerns, in part, because of the intention to motivate people to seek out genetic tests. We have explored the potential impact of such advertisements and argued for post-marketing regulation of content to accurately describe benefits and risks.

An empirical evaluation of Internet sites that allow consumers to directly purchase genetic tests and services has been completed. The searches were

conducted in May 2002 and 105 sites were identified, including 14 sites that offered health related genetic tests.

**Results:**

**Objective 1:** The central normative issue implicit in the development of cystic fibrosis newborn screening programs relates to the balancing of benefits with risks. The primary benefits are related to increased height based on nutritional interventions. The main risks are related to the anxiety created in false positive families who are identified as carriers. Most of the screening programs have been designed to maximize detection of true positives (including those CF patients at reduced risk of malnutrition because of mild alleles) without explicit regard for the number of false positives. We illustrate a hypothetical cohort where the identification of one additional CF patient would require the identification of 100 false positive families. This balancing is rarely acknowledged and we have attempted to both make it explicit and to argue for a greater tolerance for missed cases in order to reduce the burden on false positives.

While pharmacogenomic tests have a distinct purpose related to improvement of safety and efficacy of drug use, the ethical issues are not directly related to this distinction alone. We have identified specific characteristics for any genetic test that can help in the assessment of ethical issues related to risks and benefits. These characteristics include the options for interventions, scale of testing, predictive value, potential to reveal additional heath information, and risk for stigmatization. Some pharmacogenomic tests have a very favorable risk/benefit ratio while others may not. For example, a genetic test for dopamine receptor alleles to tailor smoking cessation treatments raises issues related to predictive value and stigmatization that could increase the risks of using these tests.

**Objective 2:** This project is still in the data collection phase.

**Objective 3:** The project on tailoring informed consent has been based on identifying specific characteristics that influence the medical benefit and the psychological and social implications of a test. These characteristics include the purpose of the test, predictive value, and efficacy of interventions, social environment, and pleiotropy. When these characteristics point to a profound medical benefit (such as PKU newborn screening), then the consent process should include a succinct disclosure of information, and the nature of the discussion should be to make an explicit recommendation. When the psychological and social implications are profound (such as predictive testing for Huntington disease), the information disclosure must address the contributing characteristics, and the nature of the discussion should be to help the patient make a decision consistent with his values and life circumstances. However, most tests have some combination of medical benefits and psychological implications (such as predictive testing for hemochromatosis or BRCA), and thus the consent process is a hybrid of the previous two approaches.

This approach points out that there can be a range of consent strategies based on the characteristics of the test. More importantly, it speaks to issues related to multiplex testing, whether for newborn screening, or for adult onset diseases. When a panel of diseases falls into different categories, the consent process should still be robust enough for the test with the most significant psychological and social implications. More importantly patients should be able to decline those tests on a panel that a patient feels in not in their interests.

**Objective 4:** The evaluation of the use of the "achondroplasia case study" pointed out that the desire for people with achondropsia to request terminations of fetuses with normal stature is rarely framed as speculative. This contradicts the limited empirical data that this desire is not common and has the potential to contribute to stereotypes of a population who already face significant social stigmatization.

"Lethality" is used in pediatric practice to describe children with severe neurological compromise who also have correctable medical and surgical problems. We observed that in some cases, the shortened life span may be the result of the decision not to correct the medical and surgical problems. We argue that these treatment decisions may be appropriate, but that they should be explicitly framed as issues related to the quality of life of the child. Similar to the use of "futility" in adult medicine, lethality obscures a normative decision by attributing a clinical definition to the problem.

The evaluation of direct to consumer advertisements for clinical genetic tests involved the identification of their characteristics that might make direct advertising more problematic. These include 1) complex information, 2) a vulnerable population who may be readily influenced by marketing, and 3) lack of social consensus about the value of the product. Many genetic tests have all three features. An illustrative evaluation of some advertisements also point to exaggerations of benefits and limited information about risks. The public does not have the same degree of experience and sophistication for using genetic tests that it does with pharmaceuticals, and may be more susceptible to misinformation. This could result in people requesting and obtaining tests that have limited clinical value. We call for greater oversight of such marketing strategies and empirical assessments of the impact of advertising.

The evaluation of Internet sites for genetic services found seven sites that allowed people to order and receive results without the involvement of a clinician. This is a small number, but these are easily accessible using standard search engines. Most concerning is that some of these sites offered "non-conventional" tests as well as "remedies". These sites were for age related DNA damage and another was for susceptibility to addictive behavior. We conclude that availability of direct sales is not appropriate that this time. While involving clinicians in test ordering and results interpretation may not be sufficient to minimize the risks of

genetic testing, it provides an important safeguard for a vulnerable public. More empirical research is needed to assess consumer use and impact.

**Future Directions**

The GERA pilot study will provide data for use in designing a study powered to establish whether relative risk information will influence behavior. One of the aims of subsequent study will be to explicitly examine the impact of different approaches to informed consent and result reporting that vary in their intensity. Because much of clinical practice relies on a casual approach to informed consent, it will important to establish the "minimum" approach that allows such testing to be safe and effective. The objective of the GERA project, is not to determine whether this particular test should be used in clinical practice, but to develop a model to identify and address generic issues related to the routine use of genetic testing in primary care.

We plan to continue our conceptual work related to newborn screening with a more explicit examination of implications of multiplex testing, that use current technologies such as tandem mass spectroscopy, as well as future technologies, for considering the criteria for the introduction of new tests. We also will examine how a broader range of tests may influence the approach for informed consent.

We plan to explore the empirical impact of the commercialization of clinical genetic services by looking more closely at the recent experience of direct-to-consumer advertising for BRCA testing. One hypothesis is that individuals will seek out and obtain testing when they are not at high risk, with resulting diminished positive predictive value, which will make the interpretation and clinical recommendations more ambiguous.

Another aspect of advertising that interests us is the increase of "Ashkenazi disease panels" that are marketed to physicians and patients. These panels include testing for heterogeneous clinical conditions. We plan to evaluate what specific tests are offered by each laboratory and the ability of patients to decline specific tests. Our hypothesis is that some advertisements and marketing packages may exploit community identification to increase test uptake. In some cases, no options are offered to decline specific tests, and in others, financial incentives are offered.

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